Exhibit 189

REDACTED

VALSARTAN LITIGATION

RESPONSE TO PETITION FOR CLASS CERTIFICATION & MEDICAL MONITORING COMPLAINT

REPORT OF MICHAEL BOTTORFF, Pharm. D.

This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions I offer in this report is given to a reasonable degree of scientific certainty and is based on the methods and procedures of science, my knowledge of recognized scientific principles and methodology reasonably relied upon by members of my profession, the materials and literature I have reviewed in connection with this litigation, as well as my education, training, knowledge, and experience. Citations to specific reference material are offered in this report, where I believe it necessary to cite a specific source. Otherwise, my opinions are derived from a combination of reference sources, my own experience, and general scientific knowledge. The facts and data set forth herein are the types of facts and data that I and other experts in the fields of pharmacology and pharmacokinetics reasonably rely upon. Each opinion in this report is offered to articulate a sufficiently reliable basis for my opinions concerning this case. This report is not meant to be an exhaustive recitation of all of my opinions in this case.[1]

I. CREDENTIALS AND EXPERIENCE

I am currently employed at the College of Pharmacy at Manchester University in Ft. Wayne, Indiana as an adjunct professor, and at the University of Cincinnati in the same faculty position. I have been employed by Manchester University since 2015, and hold the rank of Full

[1] This report is not intended to be an exhaustive recitation of all of my opinions in this litigation, and I expressly reserve the right to amend or supplement this report to offer additional opinions, including opinions on liability, specific causation, damages, or other defenses, at the appropriate stage of litigation.

Professor. A copy of my current *curriculum vitae* detailing my education, academic and professional experience, editorial services, professional affiliations, and publications, is attached as **Exhibit A**. I received a Bachelor of Science degree with honors in Industrial Management from the Georgia Institute of Technology in 1976. I completed my Doctor of Pharmacy in 1981 at the University of Kentucky. My postdoctoral training (1981-1983) was at the Albert B. Chandler Medical Center at the University of Kentucky in the College of Pharmacy where I was the Chief Resident.

In my current position, I teach or have taught medical students, pharmacy students and residents pharmacology, including cardiovascular pharmacology. I provide information on how pharmaceutical drugs work in the body and how drugs interact with the body's systems so they may better understand how to select the best drug for a particular patient's needs. Since their introduction into the U.S. market, sartans are drugs that I have taught my medical and pharmacy students and/or residents when discussing the treatment of hypertension and heart failure. "Sartans" are Angiotensin Receptor Blockers ("ARB"), including, for example, valsartan, losartan, and irbesartan (hereafter "sartans"). I also instruct on issues related to pharmacology, metabolism, clinical benefit, toxicities, and drug interactions for a variety of pharmaceutical drugs, including for the sartans described above. I have a 30 year history of rounding on hospital in-patients with cardiologists treating patients receiving drug therapy for hypertension and heart failure, and I have lectured extensively on cardiovascular topics for nearly 40 years.

In addition to my current teaching responsibilities, I continue to author textbooks and journal articles, as well as give presentations on cardiac pharmacotherapy and pharmacologic principles. I have been awarded numerous research grants and have published 36 original

research articles in peer-reviewed journals in my field, along with dozens of abstracts related to cardiovascular pharmacotherapy and pharmacokinetics. Most of these studies have incorporated the use of pharmaceuticals, which has required specific knowledge of the pharmacokinetics and pharmacodynamics of these drugs.

Prior to accepting my position at Manchester University, I was a Professor and Chair of the Department of Pharmacy Practice for 4 years at the South College School of Pharmacy, and held a similar position prior to that at the School of Pharmacy at the University of Charleston in the Department of Pharmacy Practice. I was also Co-Director of PharmUC, a Cardiovascular Risk Reduction Clinic offering anticoagulation, lipid, diabetes, and hypertension management services. My research has focused on cardiac and vascular function, and how cardiovascular drugs affect function. I have lectured nationally and internationally on antihypertensive drugs and drugs for heart failure, including their pharmacokinetic and pharmacodynamic properties. Prior to working at the University of Charleston, I was a professor of Clinical Pharmacy at the College of Pharmacy for 20 years at the University of Cincinnati. Prior to that, I also served as faculty at the University of Tennessee where I lectured on the practice of Clinical Pharmacy using cardiovascular drugs.

During my career, I have served on advisory boards and national speaker bureaus for several of the pharmaceutical companies that make sartans, including Merck (losartan), Bristol Meyers-Squibb (irbesartan), and Novartis (valsartan). I have received numerous awards and honors in the field of Clinical Pharmacy, and published original research, review articles and book chapters in peer-reviewed journals and books, much of which involved investigation of drug metabolism and pharmacokinetics. Additional presentations and publications on this

subject are reflected on my CV attached here. I have also participated in numerous pre-market drug studies on the mechanisms of action, absorption and distribution of pharmaceuticals in the body, and evaluation of new drugs for drug-drug interaction.

II. DISCLOSURES

I have been asked on behalf of Defendants to provide an independent evaluation of the pharmacokinetics of valsartan and N-nitrosodimethylamine ("NDMA") and N-nitrosodiethylamine ("NDEA") in this case, and in particular to respond to the recent Petition for Class Certification, including with respect to the pharmacokinetics, pharmacodynamics, bioavailability or bioequivalence of valsartan generic products containing NDMA or NDEA, as well as the opinions offered by Plaintiffs' experts Ron Najafi, Ph.D., Kali Panagos, Pharm.D, R.Ph, and Edward H. Kaplan, M.D. I will offer opinions on the background of NDMA and NDEA and valsartan, as well as general principles of pharmacokinetics, including the related topics of pharmacology, pharmacodynamics, and drug interactions. I will offer opinions on the pharmacokinetics and metabolic fate, including the absorption, metabolism, distribution, and elimination, of valsartan as well as NDMA/NDEA, and the related concept of accumulation. Further I will opine on the ANDA requirement of establishing bioequivalence with a reference brand name drug, and in particular opine on the bioequivalence of valsartan as an individual drug as well as the bioequivalence when combined with other drug products including hydrochlorothiazide and amlodipine. Finally, I will opine on whether the presence of

NDMA/NDEA in generic valsartan products would be expected to have any effects that could alter the bioequivalence, and thus the therapeutic efficacy, of valsartan generic products.[2]

The materials I have reviewed in connection with this matter are listed on **Exhibit B** attached here. I reserve the right to supplement this list, as well as to amend and supplement the opinions expressed in this report. I reserve the right to modify this report and my opinions as additional information is provided, including but not limited to additional discovery, records, expert reports, and the depositions of fact and expert witnesses. I also reserve the right to testify within my area of expertise in response to testimony from any of the plaintiffs' experts, whom I understand have not yet been deposed, or in later phases of the case involving liability, specific causation, damages or otherwise.

In addition to documents identified in **Exhibit B**, my opinions are based on my knowledge, research and experience with the pharmacology and pharmacokinetics of drugs.

My customary fee for professional services, including my review and testimony in this matter, is $500 per hour. In the last four years, I have testified in Polt et al. v. Sandoz Inc., No. 2:16-cv-02362-ER, U.S. District Court for the Eastern District of Pennsylvania, and in this Valsartan litigation.

III. SUMMARY OF OPINIONS

I provide my opinions in this report that, based on the independent pathways of metabolism and elimination, the presence of NDMA and/or NDEA in generic valsartan would not alter the bioequivalence and thus the clinical efficacy of generic valsartan, nor would it have

[2] These opinions are offered for each of the generic manufacturer defendants for whom I have been provided the bioequivalence data for their drug products which I rely upon for my opinions.

any impact on the pharmacokinetics or pharmacodynamics of valsartan generic products. Additionally, I opine that the presence of active, intended ingredients with valsartan, such as hydrochlorothiazide ("HCTZ") and/or amlodipine, would not alter valsartan bioequivalence for the same reason—there is no overlapping pharmacokinetic process. Further, based on both the amounts of NDMA/NDEA found in valsartan and the oral route of administration of valsartan, the ingestion of NDMA/NDEA from generic valsartan products in humans would be confined to, and completely metabolized by, the liver, thus sparing exposure of these compounds to any "downstream" organs. Finally, I provide the pharmacokinetic basis for describing how the ingestion of NDMA/NDEA in humans once daily would not lead to any accumulation. As a result, there is no scientific basis to assume there is any increased risk to other organ systems to support the medical monitoring proposed by Plaintiffs' expert Dr. Kaplan.

IV. METHODOLOGY FOR REPORT

In order to conduct research, write published manuscripts, give national/international presentations and teach to pharmacy, medicine and nursing students, I rely on the retrieval, analysis and synthesis of the medical and scientific literature. I used this same process to review the medical and scientific literature on the relevant issues in this litigation—and 40 years' experience conducting such processes—to derive my opinions.

Specifically, I have reviewed the FDA requirements for bioequivalence and the various generic valsartan ANDAs that led to their FDA approval as equivalent to the reference Novartis products. I have conducted a thorough literature review on the metabolic fate, metabolism, and distribution of NDMA/NDEA and valsartan. In addition, I have reviewed and provided the

mechanisms of drug interactions, and how this relates to NDMA/NDEA and valsartan bioequivalence. I have also researched and reviewed the scientific literature on the concept of drug accumulation.

V. BACKGROUND AND OPINIONS

1. Background on NDMA/NDEA Found in Valsartan

Valsartan, along with losartan and irbesartan, are FDA-approved prescription drug products that fall within the ARB drug class, used for the treatment of hypertension, or high blood pressure, and heart failure. Valsartan has been used for many years to safely and effectively treat hypertension, heart failure, and post-myocardial infarction. Valsartan is available in tablet and liquid forms and is ingested orally. It is commonly prescribed in dosage strengths of 40 mg, 80 mg, 160 mg, or 320 mg.

This litigation arises from a situation in which the unexpected impurities NDMA and later NDEA were found in certain lots of valsartan made by various manufacturers leading to recalls beginning in or around June 2018 and November 2018, respectively.

After June 2018, the U.S. Food and Drug Administration ("FDA") published NDMA testing results for finished dose products that were manufactured using various manufacturers' active pharmaceutical ingredients, or APIs. The FDA's publication included several valsartan products containing NDMA, in varying amounts:

144 **Table 1 – FDA's Testing of Valsartan for NDMA[3]**

Company	**Product (tablets)**	**Lots Tested**	**NDMA level micrograms – (mcg)/tablet (midpoint)**	**NDEA level micrograms – (mcg)/tablet (midpoint)**
Aurobindo Pharma Ltd	Amlodipine 10mg/Valsartan 320 mg	VKSA18005-A, VKSA18007-A, VKSA18001-A	Below LOD	0.02-0.09 (0.055)
Aurobindo Pharma Ltd	Valsartan 320mg	VUSD17008-A, VUSD17001-A, VUSD17009-A	Below LOD	0-0.05 (0.025)
Aurobindo Pharma Ltd	Valsartan 320mg/HCT 25mg	HTSB18001-A, HTSB18028-A, HTSB18029-A	Below LOD	0.02-0.19 (0.105)
Hetero Labs Ltd	Valsartan 320mg	VLS18049, VLS18051, VLS18050	0.33-0.44 (0.385)	Below LOD
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg	3079709, 3077618, 3079708	Below LOD	0.04-0.11 (0.075)
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	2008702	Below LOD	0.05
Mylan Pharmaceutical Inc.	Valsartan 320mg	3080009, 3080010, 3079205	Below LOD	0.07-0.16 (0.115)

[3] *See* FDA, *Laboratory Analysis of Valsartan Products*, FDA.gov, *available at* https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products (last updated May 2, 2019) (midpoint amounts added in parentheticals).

Mylan Pharmaceutical Inc.	Valsartan 320mg/HCT 25mg	3084886, 3093804, 3084862	Below LOD	0.20-0.38 (0.29)
Prinston Pharmaceutical	Valsartan 320mg	344B18027, 344B18028, 344B18029	15.18-16.30 (15.74)	Below LOD
Prinston Pharmaceutical	Valsartan 320mg/HCTZ 25mg	611B18025, 611B18026, 611B18027	13.18-20.19 (16.69)	Below LOD
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg	26X053, 26X054, 26X055, 26X051, 26X044, 26X048	Below LOD	0-0.03 (0.015)
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	22X045, 22X046, 22X047, 22X038, 22X041	Below LOD	0-0.03 (0.015)
Teva Pharmaceuticals	Valsartan 320mg	1240425A, 1247282M	7.92-16.55 (12.24)	Below LOD
Teva Pharmaceuticals	Valsartan 320mg/HCTZ 25mg	1217576M, 1217577M, 1217578M	6.94-10.35 (8.65)	0-0.77 (0.385)
Torrent Pharmaceuticals	Amlodipine 10mg/Valsartan 320 mg/HCTZ 25mg	BBX2E001, BBX2E002, BBX2E003	10.24-11.53 (10.89)	Below LOD
Torrent Pharmaceuticals	Valsartan 320mg	BV48D001, BV48D002	0.56-0.62 (0.59)	1.12-1.22 (1.17)
Torrent Pharmaceuticals	Valsartan 160mg	BV47D001	0.45	1.31

For values that report a range for any manufacturer, I have included (in parentheses) the calculated midpoint for that range of values.

2. Principles of Pharmacokinetics

a. What is Pharmacokinetics

Pharmacokinetics is the description of what happens to a drug/chemical as it passes through the human body. The steps involved in this journey through the body are absorption, distribution, metabolism, and elimination, often abbreviated ADME. For the majority of drugs, these processes have been clearly identified and expressed in mathematical terms that describe the rate and extent of each step.[4]

i. *Absorption: the various ways in which xenobiotics enter the body*

Most drugs are introduced into the body by either an oral (by mouth) or injected (intravenously or IV usually). Other drugs may be introduced through inhalation, transdermally, sublingually or rectally. Absorption, metabolism, distribution, and elimination are dependent on the route of administration; thus, as oral administration is the only route of administration in the issues at hand, I will only address absorption with oral administration.

When administered orally, for the drug to eventually reach the blood stream (the systemic circulation), the drug must first be released from the dosage form (e.g., tablet, capsule) then absorbed across the gastrointestinal tract. Although most drugs are released from their dosage form in the acidic environment of the stomach, the stomach is not the most common area for absorption into the body. The design of the upper small intestine is such that most drugs (and nutrients) are absorbed there. Once absorbed across the small intestine, adjacent blood supply transports the drug into the portal circulation directly into the liver. The

[4] Caldwell, *An introduction to drug disposition: the basic principles of drug absorption, distribution, metabolism and excretion* (1995); Bottorff MB et al., *Drug concentration monitoring*, in: Progress in clinical biochemistry and medicine, Springer-Verlag, Heidelberg 1-16 (1988).

liver is a complex organ providing a number of important physiologic functions that include drug metabolism as a detoxification step. This is a protective system that gives the liver a chance to metabolize/detoxify ingested compounds before releasing the drug and/or its metabolites into the systemic circulation for ultimate elimination. This metabolic step prior to a drug reaching the systemic circulation is termed pre-systemic metabolism or first-pass metabolism. Graphically, for illustration purposes, this process is seen here:

Figure 1.

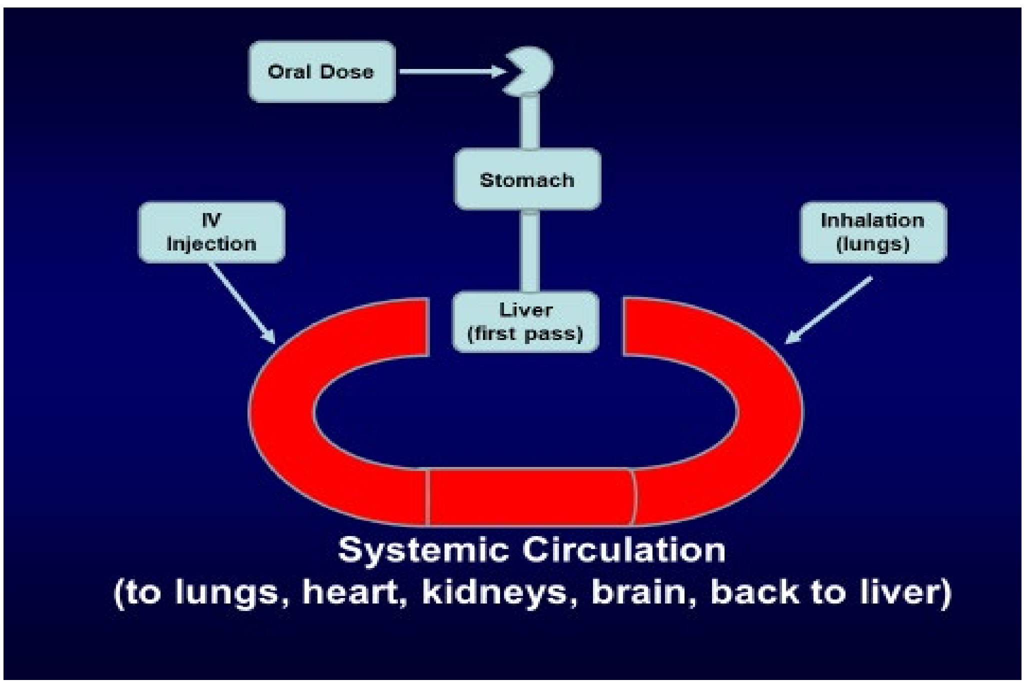
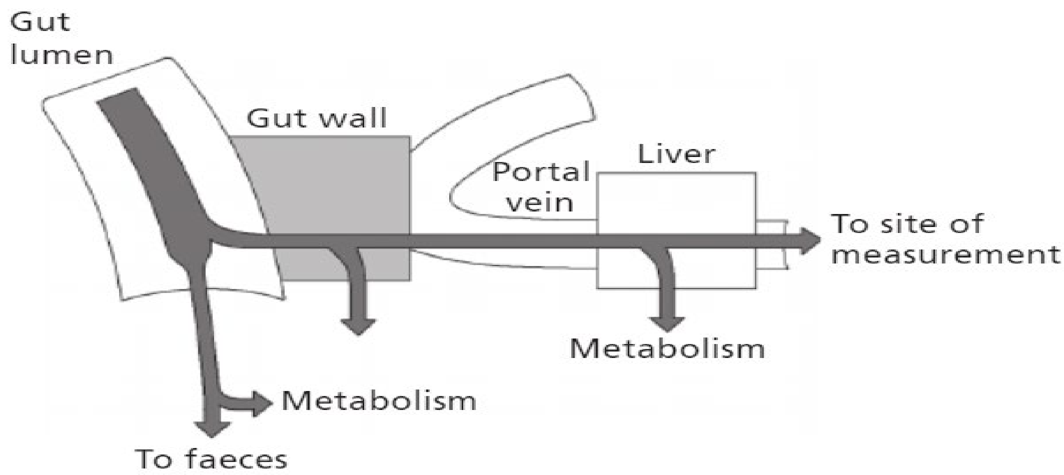


Figure 2.[5]



ii. Metabolism of orally administered drug products relies on the liver to release the active pharmaceutical ingredient.

A major function of the liver is to metabolize drugs, which are usually fat soluble, to a metabolite that is more water soluble and more easily eliminated from the body through the kidney. These metabolism steps are divided into two main types, Phase 1 and Phase 2 reactions. Phase 1 metabolic reactions are accomplished by a super family of metabolizing enzymes called the cytochrome P450 system ("CYP").[6] There are over 50 individual CYP enzymes identified in humans. Each individual CYP has a specific role in metabolism of a specific drug, called substrate specificity, so the individual CYPs have a name that identifies its specificity. Examples include CYP3A4, CYP2D6, and CYP2E1. The majority of these CYPs are found in the liver, however many of the CYPs are also located in the gut wall where some drug metabolism may occur prior to reaching the liver, depending on the presence or absence of

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[5] Thelen K et al., *Cytochrome P450-mediated metabolism in the human gut wall*, J. Pharm. Pharmacol. 61:541-558 (2009).
[6] McDonnell AM, Dang CH, *Basic review of the cytochrome p450 system*, J. Adv. Pract. Oncol. 4(4):263-268 (2013).

that individual CYP in the gut wall. Thus, one component of first-pass metabolism (see Figure 2) may occur as drugs are absorbed across the gut wall prior to another round of metabolism by the liver. Other sources of CYP are the lungs, kidney, and brain, where local drug metabolism could occur if the parent compound reaches that organ by overloading the capacity of first-pass metabolism.

Phase 2 reactions are termed conjugation reactions in that the parent compound has a chemical structure added to the drug to make it more water soluble for renal elimination. These include glucuronidation, sulfation, acetylation, and others. In many cases, a drug is first metabolized by the CYP system in a Phase 1 reaction then undergoes a second round of Phase 2 metabolism, rendering the drug's metabolites more readily excreted by the kidney.

iii. Distribution: dependent on dose and route of administration

Drug distribution for drugs administered in tablet form occurs if the drug gets by first-pass metabolism and reaches the systemic circulation, where it is transported by the blood stream to various organs and tissues. For a drug with higher affinity for plasma proteins (protein binding), the amount of drug escaping first-pass metabolism would have a more limited tissue distribution as the drug prefers to remain bound to the proteins in the blood stream itself. Unbound drugs, or drugs with little to no protein binding, are then free to interact with the various tissues and organs where the clinical effects are seen. The drug then binds to receptors, enzymes or other target sites that result in the action (beneficial, toxic) of that drug. This is termed the drug's pharmacology or pharmacodynamics, or the effect of the drug on the body. In some cases, the drug metabolites actually have activity at a target site as well.

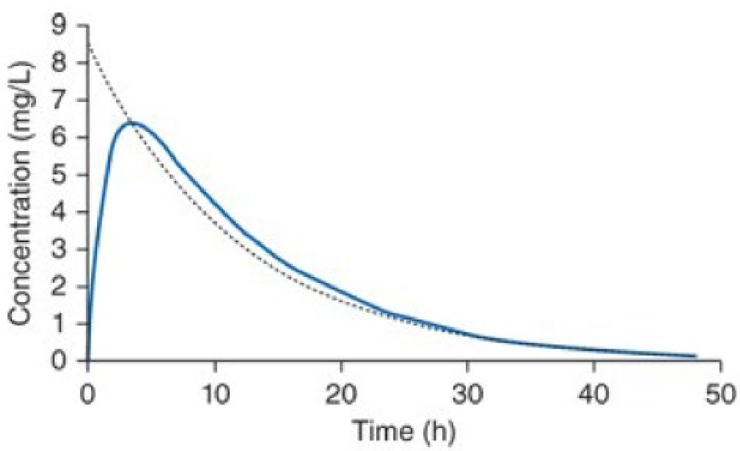
iv. Elimination: dose and route dependent

Drugs from oral administration or their metabolites are usually filtered by the kidney and eliminated from the body in urine. Some drugs may be eliminated in the feces; this could occur for a portion of a drug that is never completely absorbed across the gut wall or for a drug that is incorporated in the liver into the bile and secreted through the bile duct into the gall bladder, which dumps bile into the small intestine.[7] Other less common routes of elimination include in air vapor from the lung or in sweat.

b. Mathematically Characterizing Pharmacokinetic Processes

Once a drug has been administered orally or by injection, blood and/or urine samples can be collected and the serum/urine analyzed for a drug over a specified period of time to numerically characterize the various steps in the ADME process. This produces a concentration versus time plot as in Figure 3 below.

Figure 3.[8]



Source: Larry A. Bauer: Applied Clinical Pharmacokinetics, 3rd Edition
www.accesspharmacy.com

[7] Dobrinska MR, *Enterohepatic circulation of drugs*, J. Clin. Pharmacology 29:577-80 (1989).
[8] Bauer LA, Applied Clinical Pharmacokinetics Ch. I: *Basic Concepts* (3d ed. 2014).

For an orally administered drug, represented by the solid blue line in Figure 3, there will be a rise in serum concentrations reflecting the rate of absorption until the rate of distribution and elimination exceeds the rate of absorption and drug concentrations begin to fall. The highest measured drug concentration is called the peak and the rate of drug decline in the serum can be reflected by something called the half-life—that is, the time it takes for a drug concentration to be cut in half. There are three additional points of interest in Figure 3 above: 1) the dashed line represents an injected dose of a drug (or some other non-oral route), which would have no absorption phase and would also bypass the first-pass metabolism of that drug, making it more readily distributed to tissues outside the liver; 2) the area under the concentration time curve ("AUC") is a reflection of systemic exposure to the drug and related to the overall extent of bioavailability in the case of an orally administered drug (bioavailability would essentially be 100% for a drug administered by the IV route); and 3) an orally administered drug with extensive first-pass metabolism would not result in significant extrahepatic distribution, elimination or pharmacologic effect and no or little drug would be measured in the blood after administration.

<u>c. Linear vs. Non-Linear Pharmacokinetics</u>

When doubling the dose of a given drug results in a doubling of the AUC, or systemic exposure, that drug is deemed to exhibit linear pharmacokinetics. Since drug dose and elimination are the primary determinants of the overall AUC, a drug displaying linear pharmacokinetics implies that the metabolic process for that drug has not been exceeded. If, however, the increase in drug dose results in a disproportionately larger increase in AUC, then the metabolic capacity of the drug has been exceeded and a larger than proportional increase

in systemic drug exposure will result. This is often seen with drugs having significant first-pass metabolism; once the metabolic capacity of the liver is exceeded by a high enough dose, then a disproportionate rise in serum concentrations and systemic exposure would result. When drugs are given in doses that do not exceed the metabolic capacity, the elimination rate is constant and it takes the same amount of time to eliminate the drug based on its half-life. This is termed first order elimination and 95% of drugs are given in doses that result in a first order pharmacokinetic profile. For example, for a drug with a 6 hour half-life, it would take 6 hours for drug serum concentrations to reduce from 100 nanograms per milliliter to 50 nanograms per milliliter and the same 6 hours to reduce from 10 nanograms per milliliter to 5 nanograms per milliliter.

However, if the elimination system has been saturated with a higher dose, then the dose has exceeded the metabolic capacity for that drug and a maximum amount of drug will be eliminated in a fixed rate until the concentrations go below the maximum threshold, and first order pharmacokinetics takes over. Thus, doses that produce linear pharmacokinetics are eliminated in a first order fashion, and doses above the metabolic capacity display non-linear elimination and zero order pharmacokinetics.

d. Pharmacokinetic Parameters

As a result of mathematically describing the pharmacokinetics of a drug, there are several calculated parameters unique to an administered drug at a particular dose. The rate of elimination is termed half-life—the time it takes for drug concentrations to fall by 50% during a first order pharmacokinetic process. The peak concentration, Cmax, reflects the highest measured drug concentration after an oral dose and is a reflection of the rate of absorption.

The AUC is a measure of the overall systemic exposure to a drug. When observed serum concentrations are compared to the dose given, there is an apparent volume of distribution, Vd, usually expressed in liters, reflecting a hypothetical volume that the drug dose was distributed in. It is a reflection of how much the drug distributes into the body. Bioavailability is another term that reflects what percent of an orally administered drug reaches the systemic circulation. Drugs with extensive first-pass metabolism will have a lower bioavailability than drugs that have less extensive first-pass metabolism. Finally, when comparing the bioavailability of one drug to another, as in the case of a generic drug versus the original drug, the term bioequivalence is used to reflect how similar one drug product is compared to another, utilizing the Cmax and AUC as markers of the rate and extent of bioavailability.

All of the pharmacokinetic terms may be determined after a single dose or in some cases after multiple doses. When enough multiple doses are administered such that the rate of drug being given is matched by the rate of drug elimination, then the drug is said to be at "steady state," and the rise and fall of drug concentrations with each dose will be the same, dose after dose.

e. Mechanisms of Drug Interactions

Drug-drug interactions can occur when two co-administered compounds interfere with the ADME of one or both of the drugs administered together. Drug concentrations could rise, leading to drug toxicity, or fall, leading to a loss of drug effect. Given that the vast majority of administered drugs are lipid soluble to varying degrees and require the CYP450 system for elimination, competition for a specific CYP enzyme is the most common mechanism of drug

interaction.[9] The drug with higher affinity for the specific CYP enzyme will be preferentially metabolized to the detriment of the other drug, increasing its drug levels to potentially dangerous levels. However, for drugs not as dependent on CYP enzymes, or for drugs with different CYP pathways, no significant drug interaction would be expected. Thus, the identification of each compound's specific metabolic fate is important to predicting when two co-administered compounds might interact, or not.

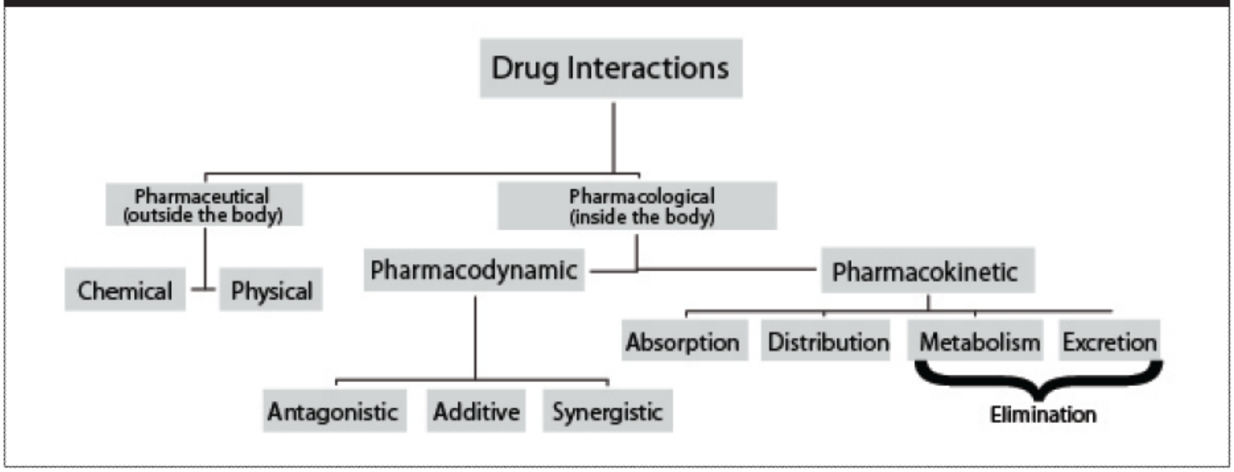
Drug interactions can be classified in many ways, but the most common way is to characterize the potential interaction as being either pharmaceutical (occurs in the dosage form outside the body before ingestion) or pharmacologic, these being either pharmacokinetic or pharmacodynamic in nature.[10] These potential mechanisms of drug interactions are depicted below:

[9] Bottorff MB, *Safety considerations of statin therapy*, Cardiology Review 16:5-9 (1999); Worz CR & Bottorff MB, *The role of cytochrome P450-mediated drug-drug interactions in determining safety of statins*, Expert Opin. Pharmacother. 7:1119-27 (2001); Bottorff MB, *Statin safety and drug interactions: clinical implications*, Am. J. Cardiol. 97:27C-31C (2006).

[10] Scott, et al. *Mechanisms of Drug Interactions*, Pharmacy Tech Topics, Vol. 18, No. 3 (July 2013).

Figure 4.[11]

Figure 1. Classification of drug interactions[13]



Pharmaceutical interactions may occur when there is a chemical reaction between components in the dosage form, such as a drug precipitating into a salt in an IV bag, or a physical reaction, as when a drug (like nitroglycerin) is degraded in the presence of light. There are no articles in the scientific literature demonstrating that the presence of NDMA/NDEA in a valsartan product produces either a chemical or physical alteration of the valsartan present in the dosage form.

Pharmacologic interactions occur within the body after drug administration. If the interaction is pharmacodynamic, the two compounds either antagonize each other or produce additive/synergistic pharmacodynamics effects. These are usually at the site of action, such as a receptor or an enzyme. Again, there are no data suggesting any type of pharmacodynamic interaction between nitrosamines (NDMA/NDEA) and valsartan, whose primary site of action is at the angiotensin II receptor. The vast majority of interactions are pharmacokinetic, with the

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[11] Scott, et al. *Mechanisms of Drug Interactions*, Pharmacy Tech Topics, Vol. 18, No. 3 (July 2013).

majority of those at either the metabolism or elimination step of the drug of interest. They could be during the absorption phase, and again there is no indication that NDMA/NDEA would alter the release of valsartan from its dosage form, nor its absorption through the upper small intestine. Likewise, when valsartan is taken up into the liver by the transporter protein OATP1B1, there is no indication that nitrosamines would alter that step in valsartan elimination. The same concept applies to valsartan elimination from the liver either through its small amount of metabolism by CYP2C9 or its biliary excretion by MRP2. Thus every step of valsartan pharmacokinetics occurs independently of NDMA/NDEA, with no overlapping steps in the pharmacokinetics or pharmacodynamics of valsartan. Therefore, I conclude that the presence of nitrosamines in any valsartan product does not alter its amount in its dosage form, its pharmacokinetics, or its pharmacodynamics, and therefore its bioequivalence to the branded valsartan reference product.

f. Effect of First-Pass Metabolism on Orally Ingested Drugs

Based upon the above description of pharmacokinetic processes, the ultimate disposition of an orally ingested compound will depend, to a large extent, on the dose. This is most important for compounds with a high first-pass extraction, where the dose administered orally will determine ultimate drug distribution and metabolism. If the dose is *below* the capacity of the liver to efficiently extract the drug, then what escapes the liver to the systemic circulation will be metabolites and very little parent compound. Only when the dose exceeds first-pass metabolism capacity, will unchanged drug or compound be systemically available for distribution through the blood stream, leaving the liver and being delivered to other tissues and organs. There are numerous examples of this in the medical literature: Lidocaine, an anesthetic

and antiarrhythmic drug, can only be administered intravenously for its antiarrhythmic effect because oral use is almost completely cleared by first-pass metabolism. Nitroglycerin, a long-time drug for angina, is most effective given intravenously, sublingually or transdermally, routes of administration that bypass the liver's first-pass metabolism. Only when given in large oral doses can nitroglycerin be an effective antianginal drug by overloading the first-pass metabolism of the compound. Thus, for drugs having a high first-pass metabolism, more widespread drug distribution to organs beyond the liver would be seen with non-oral routes of administration, such as sublingual, intravenous, and inhalation, among others.

3. Pharmacology vs. Pharmacokinetics vs. Pharmacodynamics

As explained above, a basic description of pharmacokinetics is how the body handles an administered compound, resulting in a mathematical characterization of these processes using ADME. Pharmacodynamics is what the drug or compound does to the body. Included in pharmacodynamics is how a particular drug works, through what mechanism(s). That is the drug's pharmacology. For example, is it a blood pressure lowering drug acting on the renin-angiotensin system, or is a blood pressure drug blocking the body's beta-receptors?

4. Metabolism of Valsartan

a. The pharmacologic properties of valsartan have been thoroughly studied and therefore are well understood.

Valsartan has been in clinical use for more than three decades, and thousands of research studies ranging from in vitro pharmacology, animal pharmacology and toxicology, and human studies have been conducted on this drug. The following summarizes important features of valsartan, most of which have been known for decades.

As mentioned, valsartan is one of several drugs in the classification of ARBs. ARBs were a logical follow-up to the angiotensin converting enzyme inhibitors (ACEIs) which blocked the formation of angiotensin II, whereas ARBs block the effects of angiotensin II at its receptor, the AT_1 receptor. Angiotensin II (AII) is one of the most potent vasoconstrictors in humans and is implicated in the pathophysiology of hypertension, heart failure and certain types of kidney diseases. Thus, either blocking AII formation with an ACEI or its action at AT_1 receptors with an ARB improves patient outcomes in these important diseases. Although similar in benefit, ARBs are particularly important compared to ACEIs as they are much less likely to cause some of the ACEIs' more serious side effects, cough and angioedema. Angioedema is the more serious of the ACEI side effects and is an allergic type reaction that manifests as swelling of the face, lips, tongue and sometimes the airway, which can lead to severe shortness of breath and may require the insertion of breathing tubes.

Therefore, ARBs, including valsartan, are frequently prescribed for patients who have experienced or are at higher risk for the ACEI related side effects in patients with these important cardiovascular and renal diseases. Any disruption in therapy for safety concerns, such as the presence of NDMA/NDEA or other nitrosamines, should be carefully considered in the context of the important clinical benefit the ARB is providing, as discussed more fully below. This balance of risk vs. benefit is the cornerstone of therapeutic decision-making.

b. Valsartan Pharmacokinetics

After oral administration in humans, valsartan is absorbed into the body primarily in the small intestine (below the level of the stomach) and reaches peak plasma concentrations between two and four hours. The amount of a given dose that reaches the systemic circulation

(beyond the liver) is expressed by the term absolute bioavailability, and this ranges from 10-35%, averaging 25%.[12] This means that only ¼ of a valsartan dose, on average, actually circulates in the blood stream to reach the AT1 receptor sites, the valsartan mechanism of action. After absorption in the body, the first organ to see valsartan, the liver, uses CYP2C9 to metabolize only a very small amount, about 11%, producing an inactive metabolite.[13] Because of such a small amount of reliance on the CYP2C9 pathway, the potential for P450 based drug interactions is negligible. About 80% of valsartan is excreted unchanged and found in the feces.[14] Most of this fecal elimination comes from biliary excretion from the liver. Thus, there is very little actual metabolism of valsartan, and no significant drug interactions involving valsartan ADME have been identified. The only identified drug interactions with valsartan are pharmacodynamic in nature, meaning that drugs might cause fluid retention (such as ibuprofen or other NSAIDs) that could offset the beneficial blood pressure effects, or drugs might cause an increase in serum potassium levels, seen with valsartan, an effect also seen with spironolactone.[15] With this pharmacokinetic and pharmacodynamics profile, nitrosamines like NDMA/NDEA would not alter the pharmacokinetics of or response to valsartan since there is no common pathway of metabolism or alteration of its metabolism or effect.

[12] Flesch G, Müller P, Lloyd P, *Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man*, Eur. J. Clin. Pharmacol. 52(2):115-20 (1997).
[13] Nakashima A, Kawashita H, Masuda N, Saxer C, Niina M, Nagae Y, Iwasaki K, *Identification of cytochrome P450 forms involved in the 4-hydroxylation of valsartan, a potent and specific angiotensin II receptor antagonist, in human liver microsomes*, Xenobiotica 35(6):589-602 (2005).
[14] Waldmeier F, Flesch G, Müller P, Winkler T, Kriemler HP, Bühlmayer P, De Gasparo M, *Pharmacokinetics, disposition and biotransformation of [14C]-radiolabelled valsartan in healthy male volunteers after a single oral dose*, Xenobiotica 27(1):59-71 (1997).
[15] *See, e.g.*, Teva Valsartan package label (Rev. Dec. 2014).

Although not metabolized, following absorption, valsartan is taken up by the liver through an uptake transporter protein called organic anion transporter polypeptide 1B1 (OATP1B1). OATP1B1 is not a metabolizing protein, but transports valsartan into the liver, the first step in its biliary excretion process outlined above. Following liver uptake, valsartan excretion into bile and subsequently the feces, is mediated by another non-metabolizing transporter protein, multi-drug resistant related protein 2, or MRP2. In theory, inhibitors of either of these eliminating transporters could increase valsartan systemic exposure, although specific drug interactions through these processes have not been specifically conducted. In fact, in one study in patients with a genetic reduction in OATP1B1 activity, there was little effect on valsartan pharmacokinetics (blood levels), indicating that even if NDMA/NDEA altered this transporter protein (although never demonstrated), there would be no significant effect on valsartan drug levels or response.[16] In any event, there is no known or identified interaction with these transporters and NDMA/NDEA or other nitrosamines, so there is no known interaction of NDMA/NDEA with the hepatic uptake or biliary excretion of valsartan, and thus no know alteration in valsartan's clinical effects. Further, based on the principles of drug interactions, there is no known or expected effect of NDMA/NDEA on any of the pharmacodynamic or pharmacokinetics properties of valsartan such that the presence of NDMA/NDEA would have any effect on the response to valsartan.

[16] Maeda, *Effect of organic transporting polypeptide haplotype on pharmacokinetics of pravastatin, valsartan and temocapril*, Clin. Pharmacol. Ther. 79(5):427-439 (2006).

5. Pharmacokinetics, Bioequivalence and Generic Pharmaceutical Drug Approval by FDA

a. ANDA Process Requires Generic Drugs to Demonstrate Bioequivalence with Brand Drug

The FDA has authority to approve generic drugs through its Abbreviated New Drug Application ("ANDA") process.[17] Generic drugs generally are the same as the branded drug in terms of active ingredient, dosage form, strength, route of administration, quality, performance characteristics, and labeling for any intended indications. Once these dosage form characteristics are demonstrated in the sponsor ANDA, the approved generic drug will be added alongside the innovator original branded drug and be listed in the *FDA's Approved Products with Therapeutic Equivalence Evaluations*, also known as the Orange Book. The submission process is termed abbreviated because the sponsor of a generic drug is generally not required to conduct and include additional preclinical (animal) or clinical (human) safety and efficacy trials, and is instead granted approval status based on the safety and efficacy data previously submitted by the drug innovator or New Drug Application ("NDA") holder. However, the generic drug sponsor must demonstrate that their product will perform in the same manner as the innovator drug. The usual way for demonstrating performance in the same manner as the original product is to conduct bioequivalence studies. The generic drug sponsor will conduct these bioequivalence studies to show their product has the same rate and extent of bioavailability such that the same amount of **active ingredient** will be in a patient's blood stream in the same amount of time as that of the innovator drug.[18]

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[17] *See generally* FDA.gov.
[18] I reserve the right to supplement this report to offer complete opinions regarding bioequivalence as it relates to class action claims, liability, specific causation, damages and/or other issues during subsequent phases of discovery.

These requirements for bioequivalence were established with the passing of the "Drug Price Competition and Patent Term Restoration Act of 1984", also known as the Hatch-Waxman Amendments. Estimates are that almost 9 in 10 prescriptions today are for generic drugs. At an average cost reduction of 80-85%, approximately $5 billion is saved each week due to generic drug use.[19]

A bioequivalence study is conducted, usually in healthy volunteers, by giving a specific group of subjects the reference product at a specific dose, and, on a different occasion, the same dose of the proposed generic product.[20] Usually, only a single dose study is required as it would be more sensitive than steady-state (multiple dose) studies for accurate assessment of both rate and extent of absorption. Blood samples are drawn for a specific amount of time to measure the appearance and disappearance of drug in the bloodstream for both products. Typical pharmacokinetic parameters are calculated, such as AUC, Cmax and terminal half-life. The peak concentration, and the time it occurs after administration (Tmax), will be a reflection of the rate of absorption, and the AUC (systemic exposure) will be a measure of the extent of absorption. The average AUC for the proposed generic product is then expressed as a ratio compared to the AUC of the reference product; this is referred to as the point estimate. This ratio, or point estimate, and its 90% confidence limits, must be within 0.8-1.25 to establish bioequivalence. The point estimate and the 90% confidence limits are often expressed as percentages, such that the point estimate is usually close to 100% and the 90% confidence

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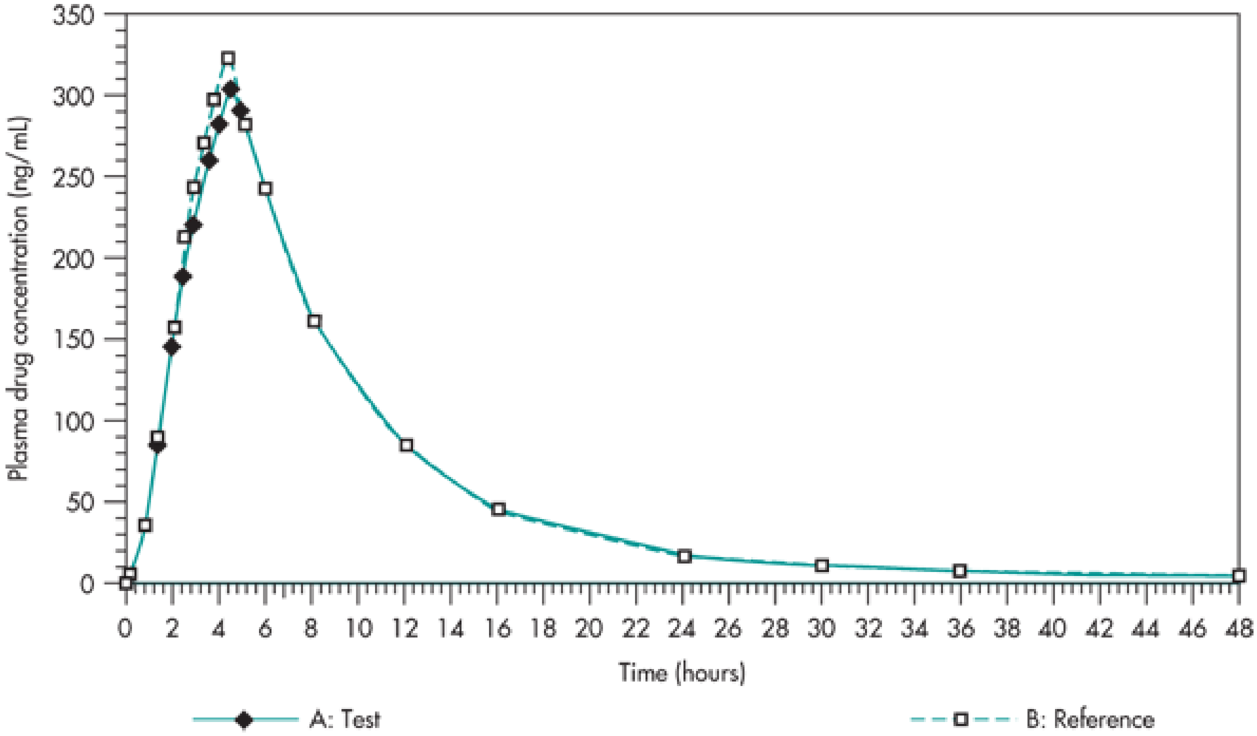
[19] Gupta R et al., *Generic Drugs in the United States: Policies to Address Pricing and Competition*, Clin. Pharmacol. Ther. 105(2):329-337 (2019).

[20] *FDA Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations* (Mar. 2014).

limits range from 80% to 125%. These upper and lower boundary limits indicate that a systemic exposure within 20% of the reference product is considered not clinically different for the generic drug.

Further, the FDA guidance also allows for conducting bioequivalence studies with products having two or more active ingredients, known as combination drug products. In this case, the rate (Cmax) and extent of absorption (AUC) must be evaluated for each active ingredient. These are then compared to the values when the active ingredients are administered with the proposed generic product and the standard or reference original combination product. A visual example of two products demonstrating bioequivalence is seen in Figure 5.

Figure 5.[21]

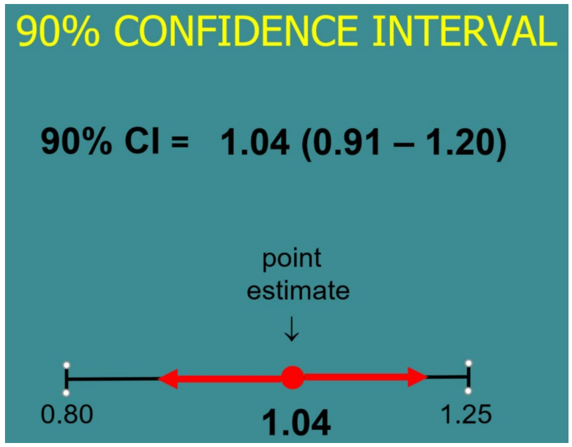


Source: Leon Shargel, Andrew B.C. Yu: Applied Biopharmaceutics & Pharmacokinetics, 7th Ed.
www.accesspharmacy.com

As stated above, the average AUC ratio and 90% confidence limit between the two products would demonstrate bioequivalence if within the FDA specified range of 0.8-1.25 as demonstrated below:

[21] Shargel et al., *Drug Product Performance, In Vivo: Bioavailability and Bioequivalence*, *in* Applied Biopharmaceutics and Pharmacokinetics (7th ed. 2016).

Figure 6.[22]



These studies are conducted on the active ingredient(s) of the proposed formulation. In the FDA glossary of terms, an active ingredient is defined as "any component that provides pharmacologic activity or other direct effects in the diagnosis, cure, mitigation treatment or prevention of disease, or to affect the structure or any function of the body of man or animals."[23] Further, in CFR 210.3(b)(7), the FDA additionally defines active ingredients as "any component of a drug product **<u>intended</u>** to furnish pharmacologic activity …." In other words, the active ingredients are those components included to provide a known, intentional pharmacologic effect. The formulation may contain inactive ingredients. The inactive ingredients are usually tablet/capsule components (excipients, binding agents, lubricants) used to make the finished dosage form. Therefore, an FDA approved generic equivalent will have the same intentional, active ingredients that demonstrate bioequivalence to the reference standard drug, but may contain different inactive ingredients, as long as they do not interfere with achieving bioequivalence with the active ingredient(s).

[22] Henderson JD et al., *Generic substitution: issues for problematic drugs*, Southern Med. J. 94:16-21 (2001).
[23] *Drugs@FDA Glossary of Terms*, FDA.gov, https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms (last updated Nov. 14, 2017).

[redacted]

[redacted]

[redacted]

[redacted]

As would be expected due to meeting FDA requirements for bioequivalence, the FDA approval of generic valsartan products is based on the generic drug sponsor demonstrating bioequivalence to the reference product Diovan. All the above single dose studies with valsartan alone show that several generic manufacturers were able to create products that would perform as generic drugs to FDA specifications. If the presence of an impurity (unintended) or even the addition of a second active ingredient (HCTZ and/or amlodipine, as

discussed below) would alter the bioavailability of valsartan, there would need to be an established alteration in one or more of the valsartan pharmacokinetics parameters, which would then alter its bioequivalence and subsequent efficacy. Again, there would need to be an identified mechanism of the interaction, either pharmacokinetic or pharmacodynamic in nature.

ii. HCTZ and/or amlodipine do not alter bioequivalence

The two common additional active ingredients added to valsartan products are HCTZ and amlodipine. HCTZ is a mild diuretic drug whose site of action is within the kidney. It is not metabolized to any significant degree and is eliminated primarily directly through the kidney into urine.[24] Therefore, HCTZ would have no pharmacokinetic or pharmacodynamic overlap with valsartan (or NDMA/NDEA) that could result in any alteration in valsartan pharmacokinetics, bioequivalence or therapeutic response. If anything, the addition of HCTZ to valsartan is designed to have an additive effect on blood pressure with valsartan, through complementary mechanisms of action to lower blood pressure. Similarly, the addition of amlodipine to valsartan is also designed to further lower blood pressure through complementary mechanisms of action. Amlodipine is a calcium channel blocker that is primarily hepatically metabolized by cytochrome P450 3A4.[25] Thus its addition to valsartan would also not be expected to alter valsartan pharmacokinetics, bioavailability or bioequivalence since, again, there are no identified mechanisms of a drug interaction and no overlapping routes of metabolism.

[24] Mylan, Hydrochlorothiazide Tablets, USP, Package Insert (May 2011).
[25] Zhu et al., *Amlodipine metabolism in human liver microsomes and roles of CYP3A4/5 in the dihydropyridine dehydrogenation*, DMD Fast Forward (2013).

The bioequivalence studies supporting the FDA-approved valsartan ANDAs can be used to demonstrate the lack of an effect of an additional compound on valsartan pharmacokinetics and bioavailability when those compounds do not share a common pharmacokinetic or pharmacodynamic pathway that could lead to a drug interaction. The presence of either HCTZ or amlodipine in a valsartan dosage form, even when present in quantities far exceeding the amount of NDMA/NDEA in the same valsartan products, does not result in a change in valsartan bioequivalence since, as described above, there is no pharmacodynamics or pharmacokinetic mechanism for such a change.

[redacted]

[redacted]

[redacted]

iv. Bioequivalence of generic valsartan plus HCTZ with reference product Diovan HCT

There is also no change in valsartan bioequivalence when another antihypertensive, HCTZ, is added to valsartan for combined antihypertensive effects. As described above, HCTZ has no overlapping metabolism or elimination step common with valsartan, and thus no interaction altering valsartan bioavailability, pharmacokinetics, bioequivalence or therapeutic response would be expected. [redacted]

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[redacted]

[redacted]

Again, these studies demonstrate valsartan bioequivalence in the presence of HCTZ, a drug with different metabolic pathways. And, as before, HCTZ bioequivalence (data not shown) was maintained in the presence of valsartan.

v. Bioequivalence of generic valsartan plus amlodipine and HCTZ with reference product Exforge HCT

To further illustrate that ingested compounds with different metabolic pathways do not adversely affect each other's disposition and therapeutic effect, [redacted]

[redacted]

These data show that even in the presence of three compounds in milligram quantities with no overlapping metabolic profiles, the bioequivalence, and hence the desired pharmacologic/therapeutic effect of valsartan, are not altered.

vi. Evidence that compounds without overlapping metabolism do not alter valsartan systemic exposure

To further demonstrate that compounds without overlapping kinetic profiles do not interfere with each other's bioavailability, metabolism, and, thus, clinical efficacy, I have reviewed the AUC data for valsartan from all the above-cited ANDAs. I chose total AUC data (the same AUC data used to create the total AUC ratios in the tables above) to evaluate the effect on valsartan from the presence of amlodipine and/or HCTZ. The results are in the table below and are only for valsartan at a dose of 320mg under fasting conditions:

[redacted]

*Represents data from a single study

** Data from valsartan 160mg, with AUC doubled following linear kinetics

The mean values indicate that there is no demonstrable alteration in the systemic exposure (AUC) to valsartan whether taken alone or with drugs like amlodipine or HCTZ, neither of which share a metabolic fate. The ratio of the highest systemic exposure, in this indirect comparison, to the lowest systemic exposure is only 11% different, a clinically meaningless amount and is more readily explained by the indirect nature of the comparison, in that these studies were done in different normal volunteer populations (North America, India) with the use of similar, but not identical, analytical methods. Thus, I can find no evidence in the bioequivalence studies that the presence of milligram quantities of additional antihypertensive agents having different metabolic profiles results in any alteration in the systemic exposure to valsartan. Therefore, I also conclude that the presence of NDMA/NDEA in quantities a thousand fold lower, and without overlapping or competing metabolic fates, would not be able to alter the systemic exposure to valsartan, thus providing the expected pharmacologic response to valsartan in the presence of these impurities.

c. Plaintiffs' Claim That the Presence of NDMA/NDEA Impurities Would Alter Bioequivalence Is Not Scientifically Founded and Is Inconsistent with the Bioequivalence Data Approved by FDA.

I have reviewed the Expert Declaration of Ron Najafi, Ph.D., opining that valsartan which contained NDMA or NDEA in it was not the same as the branded valsartan products, and the Expert Report of Kali Panagos, Pharm.D, R.Ph, opining that generic valsartan containing NDMA or NDEA is not the same as the brand name medication, that equivalence is "nulled" with respect to such medication, and that the generic valsartan is not bioequivalent in accordance with its FDA approval and information contained within FDA's "Orange Book."

These claims assert or imply that the presence of either NDMA or NDEA (or both) somehow alters the bioequivalence of valsartan. As demonstrated by the lack of overlap in the absorption, metabolism and elimination pathways between valsartan and following the outlined principles of drug interactions, there is no scientific evidence that would indicate any such interaction or any such loss of bioequivalence and thus generic valsartan would retain its safety and efficacy.

I have reviewed the FDA-approved ANDA data for valsartan, valsartan plus HCTZ, valsartan plus amlodipine, and valsartan/amlodipine/HCTZ for the various generic manufacturers of valsartan listed above. The FDA approval for these generic products was, in part, based on demonstrating that the intended, active ingredient(s) had bioavailability studies that fell well within the FDA parameters for meeting bioequivalence to the reference products Diovan, Diovan HCT, Exforge and Exforge HCT. It is my opinion that the presence of NDMA and NDEA would not alter the validity of these FDA approved generic equivalents, based on the complete lack of overlap in any of the pharmacokinetic processes of valsartan when compared to the metabolic fate of either NDMA or NDEA as described below.

I further disagree with Dr. Najafi's opinion that valsartan containing either NDMA or NDEA would not be "chemically equivalent" to the branded products Diovan and/or Exforge. Notably, "chemical equivalence" or "chemically equivalent" is not a phrase used in FDA regulations and guidance documents governing NDAs and ANDAs, nor is it a phrase used by the scientific community. Dr. Najafi cites as his references for this statement the *FDA Guidance for Industry: Changes to an Approved NDA or ANDA*[26] and *FDA Guidance for Industry: M7(R1):*

[26] *FDA Guidance for Industry: Changes to an Approved NDA or ANDA* (April 2004).

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk[27]. I have reviewed these FDA Guidances and have found no such term in either guidance document. I assume Dr. Najafi is using this term to indicate that the presence of NDMA or NDEA would somehow chemically alter generic valsartan such that it would affect its structure, bioavailability or bioequivalence to the reference products, which would then reduce its efficacy. However, as stated in my report (above), such an interaction that would render generic valsartan "not chemically equivalent" would either need to be pharmaceutical (before administration to the patient) or pharmacological (after administration).[28] First, there is no evidence of a pharmaceutical interaction that either NDMA or NDEA would degrade or alter the structure of valsartan in the dosage form prior to administering to a patient; thus, the administered generic valsartan dosage form would contain the "chemically equivalent" amount of valsartan stated in the approved ANDA. Second, in the absence of such a chemical alteration, the alternative would be that Dr. Najafi is suggesting that the presence of NDMA/NDEA would reduce the effectiveness of generic valsartan by the pharmacologic type of drug interaction. As I have detailed in my report, there is no overlapping or competing mechanism for any of the pharmacologic processes of valsartan or the nitrosamines, neither pharmacodynamic nor pharmacokinetic. Therefore, I do not agree with Dr. Najafi that the presence of NDMA/NDEA in generic valsartan products creates a "chemically inequivalent" situation. Thus, Dr. Najafi's opinion regarding lack of "chemical equivalence" is both unsupported by his own analysis as well as refuted by my analysis in this report.

[27] *FDA Guidance for Industry: M7(R1): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018).
[28] *See* Figure 4 *supra*.

6. Metabolism and Pharmacokinetics of NDMA and NDEA

NDMA and NDEA have the following chemical structures:

Figure 7.[29]

N-Nitrosodimethylamine (NDMA) N-Nitrosodiethylamine (NDEA)

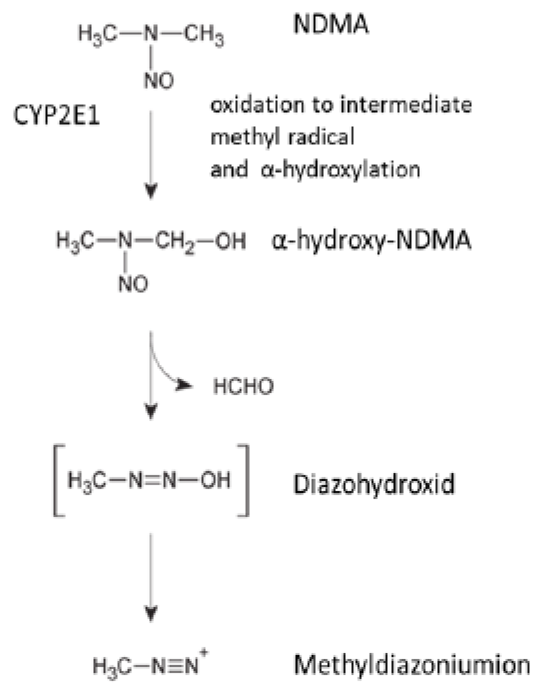
These two compounds and others are in a structural category called nitrosamines and are produced in the drug manufacturing process by a chemical reaction between amines (a single nitrogen derivative of ammonia) and nitrous acid.

a. Metabolic fate of NDMA/NDEA

There are two identified metabolic pathways for the metabolism of NDMA, seen below, which also apply to NDEA.

[29] *FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs* at 4, fig. 2 (Sept. 2020).

Figure 8.[30]



The alpha-hydroxylation pathway produces the methyldiazonium ion, which binds with a segment of DNA to produce the primary mutagenic and carcinogenic substance, O^6-methyl-guanine.[31] A key step in this metabolic activation to a potential carcinogen, is the hydroxylation of NDMA/NDEA by cytochrome P450 pathways—CYP2E1 is used almost exclusively for NDMA, and both CYP2E1 and CYP2A6 are used for NDEA.[32] The methyldiazonium ion is too unstable to escape from the cell in which it is generated, and therefore the carcinogenic potential would be

[30] EMA, *Assessment Report: Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group* 15 fig. 7 (2019).

[31] Liteplo RG et al. (WHO), *Concise International Chemical Assessment Document 38: N-nitrosodimethylamine January 2002 IPCS Concise International Chemical Assessment Documents* (2002).

[32] Kushida H et al., *Metabolic activation of N-alkylnitrosamines in genetically engineered salmonella typhimurium expressing CYP2E1 or CYP2A6 together with human NADPH-cytochrome P450 reductase*, Carcinogenesis 21(6):1227-32 (2000); Bellec G. et al., *Cytochrome P450 Metabolic Dealkylation of Nine N-nitrosodialkylamines by Human Liver Microsomes*, Carcinogenesis 17(9):2029-2034 (1996).

limited to the organ both receiving the NDMA/NDEA and having the requisite CYPs able to produce it.[33] Thus, the carcinogenic potential will, in part, be determined by the distribution of NDMA/NDEA to tissues with the capacity to metabolize through the CYP2E1 and CYP2A6 pathways for NDMA and NDEA, respectively, and the delivery of the nitrosamines to that organ.

Due to a known high rate of first-pass metabolism, the pharmacokinetics of nitrosamines will depend on the route of administration. Following intravenous, inhalation or intraperitoneal administration (IP), nitrosamines "skip" first-pass metabolism. Therefore, as described above, if administered through these non-oral methods, none of which is at issue in this litigation, NDMA/NDEA would be expected to reach the systemic circulation and be delivered to the various tissues and organs receiving blood flow. Since the P450 metabolism step is key to producing the mutagenic metabolite of NDMA and NDEA, the amount of drug delivered and the individual metabolic capacity of that organ will determine how much carcinogen is produced.

b. NDMA/NDEA in valsartan will not reach systemic circulation

Following the principles of first-pass metabolism, orally administered NDMA and NDEA, such as the NDMA/NDEA present in valsartan, are absorbed through the upper small intestine with a half-life of absorption of three minutes and then directly circulated to the liver for metabolism.[34] The absorption process is described as first-order, meaning that absorption is not saturable.[35] Although many CYP enzymes are found in the gut wall and are able to

[33] Pegg AE, *Metabolism of N-nitrosodimethylamine*, IARC Sci Publ. (27):3-22 (1980).
[34] Pegg AE, *Metabolism of N-nitrosodimethylamine*, IARC Sci Publ. (27):3-22 (1980).
[35] Gomez M. I. D. et al., *The Absorption and Metabolism in Rats of Small Oral Doses of Dimethylnitrosamine*, Biochem. J. 164:497-500 (1977).

metabolize a compound prior to reaching the liver, neither CYP2E1 nor CYP2A6 is found in the gut wall[36]; thus CYP-mediated metabolism of NDMA and NDEA following oral administration would be isolated to the liver, until a dose was given that exceeded the first-pass capacity of the liver[37]. Furthermore, there have been no appreciable genetic polymorphisms identified in CYP2E1 that would result in loss of function such that the metabolic capacity of the liver could be "overloaded" and result in more widespread NDMA/NDEA distribution to organs beyond the liver.[38] Oral doses at the levels detected in the generic valsartan at issue in this litigation are metabolized in the liver almost completely, preventing exposure to other tissues and organs. In other words, metabolism of NDMA/NDEA that is ingested orally—such as the NDMA/NDEA amounts found in orally ingested valsartan—is a classic example of first-pass metabolism: at oral doses, in the amounts found in valsartan products, metabolism occurs almost entirely during the compound's first pass through the liver, before it ever reaches systemic circulation.

The localization of NDMA/NDEA metabolism to the liver in doses of valsartan is further supported by studies involving administration of nitrosamines in rats. However, because route of administration so greatly dictates the methods and nature of absorption, metabolism, and distribution, including in the case of NDMA's/NDEA's metabolic fate, as demonstrated above, studies involving non-oral administration of nitrosamines in rats are not relevant in considering

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[36] Peters SA, Jones CR, Ungell AL, Hatley OJD, *Predicting drug extraction in the human gut wall: assessing contributions from drug metabolizing enzymes and transporter proteins using preclinical models*, Clin. Pharmacokinetics 55:673-696 (2016); Koskela S, Hakkola J, Hukkanen J, et al., *Expression of CYP2A genes in human liver and extrahepatic tissues*, Biochem. Pharmacology 57(12):1407-1413 (1999).

[37] Chen J, Jiang S, Wang J, Renukuntla J, Sirimulla S, Chen J, *A comprehensive review of cytochrome P450 2E1 for xenobiotic metabolism*, Drug Metab. Rev. 51(2):178-195 (2019); Tanner JA, Tyndale RF, *Variation in CYP2A6 Activity and Personalized Medicine*, J. Pers. Med. 1;7(4):18 (2017).

[38] Chen J, Jiang S, Wang J, Renukuntla J, Sirimulla S, Chen J, *A comprehensive review of cytochrome P450 2E1 for xenobiotic metabolism*, Drug Metab. Rev. 51(2):178-195 (2019).

the metabolic fate of NDMA/NDEA in orally ingested valsartan. Only studies involving oral doses of nitrosamines can provide the proper background with which to interpret and extrapolate the content of these nitrosamines in valsartan products.

7. Concept of Drug/Chemical Accumulation

Expressed simply, the concept of drug/chemical accumulation is a function of dose (input), clearance (output) and dosing interval. When the dosing interval is relatively longer than the amount of time it takes to "clear" the previous dose, then accumulation is minimal or non-existent. An often-used analogy for accumulation involves a water faucet and a funnel. The faucet flow (input) will not lead to accumulation (overflow of the funnel) as long as the input is less than the output (water leaving the funnel). Accumulation can actually be calculated based on known pharmacokinetic parameters for the compound of interest. This is done by using the following equation:

Equation 1.[39]

$$AR = \frac{1}{1-e^{-k*tau}}$$

AR represents the accumulation ratio, K is the individual compound's elimination rate constant, and tau is the dosing interval.[40] When first order pharmacokinetics apply, the K value represents the fraction of a drug eliminated per time, which remains a constant. For example,

[39] Brocks et al., *Rate and extent of drug accumulation after multiple dosing revisited*, Clin. Pharmacokinetics 49:7 (2010).

[40] E in this equation is a mathematical constant, also called Euler's number, that is the base of a natural logarithm; it converts log/exponential data into linear data, and its value is 2.718.

a K value of 0.15 Hr^{-1} represents 15% of remaining drug/chemical eliminated per hour. The reciprocal of K, the elimination rate constant, is the compound's elimination half-life, such that a K value of 0.15 would represent an elimination half-life of approximately 4.6 hours (T ½ equals 0.693/K^{el}). Thus, for our example, using Equation 1, let's assume that this drug/chemical is given every 24 hours (tau). From Equation 1, then, the accumulation ratio would be 1.03, indicating that there would only be 3% higher accumulation after multiple exposures to that compound. This makes sense, in our example, in that with once daily administration (every 24 hours) of a compound having an elimination half-life of 4.6 hours, almost all of the drug would be gone before the next exposure, thus little accumulation would occur (5-7 half-lives lead to removal of essentially all the compound).

We can apply this accumulation ratio to estimate what would happen in the case of daily exposure to NDMA. Using clearance, volume of distribution and therefore half-life data from Gombar 1990, the estimated elimination half-life across a number of species, including an estimate in a 70kg human, ranged from as short as 4 minutes up to 26 minutes (human 13 minutes). [41] Gombar used the following standard pharmacokinetic equations:

$$Cl/Vd = K^{el}$$

$$0.693/K^{el} = T\ ½$$

Now, plugging these values into the accumulation ratio equation and converting the units of half-life from minutes to hours, I tried to calculate accumulation ratios (AR) for the shortest, longest and estimated human K^{el} values for exposure once every 24 hours; however,

[41] Gombar et al., *Interspecies scaling of the pharmacokinetics of n-Nitrosodimethylamine*, Cancer Res. 50, 4366-4370 (1990).

using K^{el} that corresponds to mere minutes, compared to a 24 hour dosing interval, cancels out the equation denominator such that the AR is 1, meaning no accumulation at all. Using half-life of elimination is a way to double check this calculation; eliminating half a drug amount in minutes would indicate that there would be no detectable drug at all in a matter of a few hours, much less 24 hours between exposures (5-7 half lives of elimination leaving essentially no drug at all left). One could use the terminal elimination half-life data from Mico[42] in rats of approximately 10 minutes for NDMA and get the same conclusion; with such a short half-life of elimination given every 24 hours, there can be no pharmacokinetic-based accumulation.

Thus, with such a short elimination half-life and a once daily administration, there would be no pharmacokinetic-based accumulation of NDMA/NDEA. At these microgram doses, the rapid metabolism and elimination of NDMA/NDEA would occur entirely in the liver. Therefore, it does beg the question of whether there would be any hepatic accumulation of drug effect, since there could be no pharmacokinetic drug accumulation per se. Pegg (1981) studied the rapid formation of DNA methylation after small oral doses of NDMA in the rat.[43] Doses were below 100 mcg/kg, or below about 7mg for a single dose in a 70kg human adult. The studied dose (5 mcg/kg) closest to what humans would be exposed with daily valsartan containing 20 mcg, would still be 17x higher than the human daily NDMA exposure from valsartan. Pegg demonstrated that at the 5 mcg/kg dose, the formation of hepatic O^6-methyl guanine peaked quickly, within 15 minutes, but the adduct was completely eliminated within 3 hours. This

[42] Mico BA et al., *Low-dose in vivo pharmacokinetic and deuterium isotope effect studies of N-nitrosodimethylamine in rats*, Cancer Res. 45(12 pt. 1):6280-5 (1985).
[43] Pegg AE, Perry W, *Alkylation of nucleic acids and metabolism of small doses of dimethylnitrosamine in the rat*, Cancer Res. 41:3128–3132 (1981).

suggests that daily exposure at this dose would also not result in accumulation of potential carcinogenic material. Pegg further states in his conclusions that other investigators have shown that DNA repair mechanisms in humans can be as much as 10x higher than rats, indicating a more active DNA repair in humans compared to rats.

Thus, from both a pharmacokinetic and a pharmacodynamic (DNA methylation) standpoint, I can find no evidence of nitrosamine accumulation with daily amounts found in valsartan.

VI. SUMMARY OF OPINIONS AND CONCLUSIONS

1. The presence of NDMA/NDEA in valsartan could not have had any effect on the pharmacokinetics, pharmacodynamics, bioavailability or bioequivalence of valsartan generic products. The compounds do not share any known pharmacokinetic or pharmacodynamic mechanism. The presence of active, intended ingredients with valsartan, such as HCTZ and/or amlodipine, also did not alter valsartan bioequivalence for the same reason(s), that is no overlapping pharmacokinetic process. Thus, there is no conceivable way for NDMA/NDEA, merely by being present, to alter the bioequivalence of valsartan, and thus its therapeutic response and efficacy.

2. The levels of NDMA/NDEA FDA detected in the affected valsartan tablets when taken on a daily basis would not exceed the liver's capacity to metabolize the NDMA/NDEA contained in those tablets in first-pass metabolism and accordingly NDMA/NDEA is unlikely to reach systemic circulation or other organ systems outside the liver. Therefore there is no scientific basis to assume there is any increased risk to other organ systems which support the medical monitoring proposed by plaintiffs' expert Dr. Kaplan.

3. Based on the pharmacokinetic principles of accumulation, the daily exposure (every 24 hours) to NDMA/NDEA would not accumulate, given the known elimination half-life of these compounds.

I may use at trial any exhibits as a summary or in support of all of my opinions, including but not limited to: (1) any of the materials, or excerpts therefrom, identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; and (5) any exhibit used in or identified at any deposition taken in this litigation. If further data becomes available, I reserve the right to review it and consider whether to modify any portion of these opinions.

Dated: January 12, 2022

Michael Bottorff, Pharm.D., FCCP, FNLA, CLS